28. THE TREATMENT OF INTOXICATION WITH SELECTED ORGANOPHOSPHATES AND A CARBAMATE: COMPARISON OF DIFFERENT THERAPEUTIC APPROACHES

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ABSTRACT

The treatment of intoxications (2xLD50) with sarin, DDVP and pyridostigmine (s.c.) was studied in rats. The animals were s.c. injected with toxic chemicals and treated (i.m.) with atropine, atropine and obidoxime (omitted for pyridostigmine), sodium bicarbonate (i.p.), atropine (i.m.) and sodium bicarbonate (i.p.). The start of treatment was at the onset of convulsions. Acetylcholinesterase (AChE) activity and pH in the blood (different time intervals) and AChE activity in the frontal cortex, basal ganglia, pontomedullar part and hippocampus were determined (after death or 24 h). In intoxications with all compounds studied, rapid decrease of the blood AChE activity was observed. In the brain, AChE activity was decreased with the exception of pyridostigmine. Detected pH in the blood showed its decrease following intoxication. In sarin intoxication, the only atropine and obidoxime showed minimal therapeutic effect (10% of survival). In case of DDVP, therapeutic effect increased in following manner: bicarbonate (80% lethality)< atropine (60% lethality)< atropine and bicarbonate (50% lethality)< atropine and obidoxime (30% lethality). Therapeutic efficacy in case of pyridostigmine was increased in the following manner: bicarbonate (80% lethality)<atropine (50% lethality) <(atropine and bicarbonate (20% lethality). The results indicate that administration of bicarbonate improves the therapy of organophosphate and pyridostigmine intoxication.

INTRODUCTION

Insecticides are widely used in agriculture, medicine and industry. The most common types are organophosphates (OP) and carbamates. Accidents as well as professional and suicidal intoxications are often occurring. The usual therapy of OP intoxications is based on administration of parasympatholytics (preferably atropine) and cholinesterase reactivators (pralidoxime, obidoxime, HI-6 etc.). Therapy of carbamate intoxication is limited to atropine administration only. However, there are some data on the treatment of OP poisoning using atropine and bicarbonate without use of reactivators either in experimental animals (1) or in humans (2,3). These data are limited and are not sufficient for detailed analysis of such therapeutic approach. The aim of this study is to get a more detailed insight in such a treatment.

MATERIAL AND METHODS

Chemicals: ***Sarin was synthetized at Chemical Facility Zemianské Kostolany (Slovakia).***

DDVP was obtained from Spolana Neratovice (Czech Republic) and pyridostigmine was produced by VUFB Praha (Czech Republic).

Animals: Female Wister rats (Konárovice animal facility, Czech Republic) weighing 200 ± 20 g were used. The animals were kept in air-conditioned room (20-22 °C) on 12 light/dark cycles with free access to food and tap water.

Toxicity determination and doses: The chemicals were administered subcutaneously and survival/death of animals was registered 24/48 hours (n=4-6). Method of Weil (4) was used for determination of LD50. For therapeutic experiments, 2xLD50 (s.c.) was applied:

- Sarin – 200 μg/kg
- DDVP – 20 mg/kg
- Pyridostigmine – 12 mg/kg

Treatment: The animals were intoxicated with dose of 2xLD50 (s.c.). The start of the treatment was at the onset of convulsions (T3). For the treatment, following groups (n=10) treated i.m. were used:

- Atropine only (21 mg/kg)
- Atropine (21mg/kg) and obidoxime (25 mg/kg)
- Sodium bicarbonate (3 mMol/kg) administered intraperitoneally (i.p.)
- Atropine (21 mg/kg) and sodium bicarbonate (i.p.)
- Saline applied i.p. as a control

In the case of carbamate, the treatment with atropine and obidoxime was omitted.

Time of symptoms: Time of following symptoms was registered: salivation, disturbed ventilation, fasciculations (T2), convulsions (T3), generalized convulsions, death (T4).

Other parameters: Blood acetylcholinesterase (AChE) and pH in blood was determined before intoxication (T1), at the time of fasciculations (T2) and convulsions (T3) and after death or 24 hours (T4).

AChE activity in the frontal cortex (FC), basal ganglia (BG), hypothalamus (H) and pontomedullar area (PM) was determined in interval T4. AChE was expressed as ncat/g wet weight tissue (brain) or ncat/ml (blood) The result of determination represents 71% of AChE and 29% of butyrylcholinesterase (5).

Statistical evaluation: The results were calculated as means with standard deviation

RESULTS

Sarin intoxication: Symptoms of intoxication were observed in a very short time finishing in death in time less than 10 min. Rapid decrease of AChE activity in blood was observed. After death, AChE activity in the brain parts (with exception of BG) was demonstrated. No changes were observed in blood pH. Therapeutic interventions were not successful with slight exception of combination of atropine and obidoxime (90% lethality) (Tables 1-3).

DDVP intoxication: Symptoms of intoxication were observed in longer period in comparison with sarin as well as the time of death. Rapid decrease of AChE activity in the blood as well as in the brain parts (with exception of BG) after death was demonstrated. However, the inhibition was not so high in comparison with sarin. Tendency to decrease pH in the blood was demonstrated. Efficacy of therapeutic interventions was increased in following manner: bicarbonate (80% lethality), atropine (60% lethality),, atropine and bicarbonate (50-60% lethality) and atropine and obidoxime20-50% lethality) (Tables 1-3)

Pyridostigmine intoxication: Time of symptoms was very rapid comparable with sarin. But time of death was prolonged.

The quality of symptoms was different in comparison with organophosphates convulsions: they were similar as „springs" followed by pauses with disturbed ventilation. Rapid decrease of AChE activity in blood was similar to that observed for OP. Brain AChE was resistant to pyridostigmine. Decrease of blood pH was also observed. Therapeutic interventions were successful for 2h period – atropine 50% lethality, bicarbonate 80% lethality, atropine and bicarbonate 20% lethality, however, 24 lethality was different: 80 % lethality for atropine only and 100% lethality for the last two combinations (Tables 1-3).

DISCUSSION

From the results obtained, comparison with results of Wong et al. (1) was possible only. His experiments with DDVP followed by intravenous treatment with bicarbonate are better than ours. It can be caused by different approaches to bicarbonate administration (i.v. - i.p.), nevertheless, it seems to us that i.p route of administration can also be used. From the results can be calculated more parameters, e.g. mean time of symptoms for each experimental animal, tendency to changes in blood pH and AChE and many other information.

It is of interest that (in some cases) treatment with atropine and bicarbonate increased survival or the time of death of animals in comparison with administration of atropine alone.

Administration of bicarbonate or atropine with bicarbonate improved in some cases pH of the blood. On the other hand, blood AChE was slightly influenced by atropine or bicarbonate. Combination of atropine and obidoxime increased blood AChE in case of OP. It is very probably caused by reactivation of the blood AChE.

Inhibition of the brain AChE demonstrated relative resistance of AChE in BG against carbamates and OP. Simultaneously, high sensitivity of AChE in FC and PM was observed for OP intoxication. For carbamates, this sensitivity was not observed. It is very probably caused by low penetration of carbamates through blood-brain-barrier.

CONCLUSIONS

1. Survival of experimental animals intoxicated with DDVP and Pyridostigmine is positively influenced by administration of bicarbonate and atropine with bicarbonate. However, in case of sarin, treatment with obidoxime and atropine is slightly more effective.
2. In some cases, administration of atropine and bicarbonate prolonged time of death.
3. Blood AChE was decreased in dependence on time and symptoms of intoxication.
4. Blood pH was decreased during intoxication with OP and carbamate.
5. AChE in the brain parts was inhibited differentially depending on type of such chemicals.
6. The results allow to determine values of different parameters with high accuracy because of high number of animals in experimental groups.

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KEY WORDS

Sarin, DDVP, pyridostigmine, rat, treatment

Table 1: Survival of experimental animals

Sarin

atr	10/10	10/10
bic	10/10	10/10
Atr+bic	10/10	10/10
atr+obid	1/10	1/10

DDVP

atr	4/10	4/10
bic	2/10 (2 h)	2/10 (24 h)
Atr+bic	5/10 (2 h)	4/10 (24 h)
Atr+obid	8/10 (2 h)	5/10 (24 h)

Pyridostigmine

atr	5/10 (2 h)	2/10 (24 h)
bic	2/10 (2 h)	0/10 (24 h)
atr+bic	8/10 (2 h)	0/10 (24 h)

Table 2: Changes in blood AChE

Sarin	T1	T2	T3	T4
atr	9.92	3.00	1.70	0.25
bic	9.90	3.05	1.94	0.55
atr+bic	10.05	3.27	1.99	0.60
atr+obid	10.20	3.26	1.99	1.42

DDVP	T1	T2	T3	T4
atr	10.10	4.02	2.57	0.57
bic	10.14	3.99	2.87	0.87
atr+bic	10.12	4.03	2.58	0.81
Atr+obid	10.07	4.11	2.57	3.87

Pyridostigmine	T1	T2	T3	T4
atr	9.7	3.35	1.85	0.64
bic	9.94	3.39	2.20	1.18
atr+bic	9.74	3.15	2.10	0.83

Table 3: Changes in pH of the blood

Sarin	T1	T2	T3	T4
atr	7.338	7.325	7.321	7.318
bic	7.333	7.331	7.327	7.324
atr+bic	7.333	7.329	7.329	7.326
Atr+obid	7.329	7.329	7.323	7.327

DDVP	T1	T2	T3	T4
atr	7.339	7.285	7.232	7.269
bic	7.343	7.330	7.250	7.206
atr+bic	7.338	7.314	7.272	7.287
Atr+obid	7.331	7.313	7.293	7.247

Pyridostigmine	T1	T2	T3	T4
atr	7.334	7.333	7.325	7.241
bic	7.336	7.328	7.299	7.303
atr+bic	7.335	7.330	7.288	7.235

In all Tables, means are given only.